Editorial

Chronic hepatitis B in children in the United States and Canada: international origins place the disease burden on children even in the era of universal vaccination

Haruki Komatsu[1], Ayano Inui[2]

[1]Department of Pediatrics, Toho University Sakura Medical Center, Chiba, Japan; [2]Department of Pediatric Hepatology and Gastroenterology, Eastern Yokohama Hospital, Kanagawa, Japan

Correspondence to: Haruki Komatsu. Department of Pediatrics, Toho University Sakura Medical Center, 564-1 Shimoshizu Sakura, Chiba, Japan. Email: haruki-komatsu@chive.ocn.ne.jp.

Submitted Dec 30, 2015. Accepted for publication Dec 30, 2015.
doi: 10.3978/j.issn.2224-4336.2015.12.08
View this article at: http://dx.doi.org/10.3978/j.issn.2224-4336.2015.12.08

The disease burden of chronic hepatitis B is one of the most important global health concerns. To reduce the disease burden of chronic hepatitis B, in 1991, the World Health Organization (WHO) recommended the integration of the hepatitis B vaccine into the national immunization programs of countries with an hepatitis B virus (HBV) carrier prevalence of 8% or higher by 1995 and in all other counties by 1997 (1). The hepatitis B vaccine for infants was introduced nationwide in 184 countries by the end of 2014. Global coverage with 3 doses of the hepatitis B vaccine was estimated at 82% in 2014. In particular, the 3-dose coverage rate in the Western Pacific Region Office, which supports the highly endemic Asian countries, shows a rate of 92% (2). However, we are halfway to reaching the eradication of HBV.

In the current issue of "Journal of Pediatrics", Schwarz *et al.* reported the results of a cross-sectional analysis of children infected with HBV who were living in the United States (US) and Canada and were enrolled in the 7 pediatric clinical centers (California, Maryland, Minnesota, Missouri, Texas, Washington, and Ontario) of the hepatitis B research network (HBRN) (3). Between 2011 and 2014, a total of 343 children with chronic hepatitis B (age range, 1.0–17.8 years; male: 39%) were enrolled in this study. Of the 343 children with chronic hepatitis B in living the US and Canada, 78% and 55% were Asian and international adoptees, respectively. There were approximately twice as many female adoptees as male adoptees. In contrast, 24% of the 343 children were born in the US and Canada. Moreover, 97% of the children with chronic hepatitis B had international origins with the child or a parent having been born in other counties. Of the 227 children with a specified mode of transmission, 98% were infected via vertical transmission. The HBV genotypes of the 230 children with available results were as follows: A, 5%; B, 43%; C, 32%; D, 16%; E and multiple, 4% (*Table 1*). Of the children infected with genotypes B and C, 98 and 96% were Asian, respectively. Compared to the other HBV genotypes, the frequency of HBeAg positivity and the levels of HBV DNA were significantly higher in children infected with genotypes B and C. Although this was not a longitudinal study, HBeAg positivity and HBV DNA levels declined with age. This investigation highlights new insights regarding HBV infection in children.

First, the control and management of imported chronic hepatitis B, such as through immigrants and adoptees, is extremely important in children in North America, similar to adults. In parallel with the pediatric study, the HBRN performed an adult cohort study using the same methods (21 clinical centers in the US and Canada). A total of 1,625 subjects with chronic hepatitis B (median age: 42 years, male: 51%) were enrolled in this study (4). The table shows the results of both studies performed by the HBRN. Of the 1,625 subjects, 72% were Asian, of whom 92% were born outside of North America. In addition, 15% of the cohort was black, of whom 70% were born in Africa. Of the adult cohort, 60% were vertically infected. The HBV genotypes were as follows: A, 18%; B, 39%; C, 33%; D, 8%; other, 4%. Although there was a small difference in the ratio of gender between the two studies because of the adoptees, both studies showed the same distribution

Table 1 Race and HBV genotype of the patients with chronic hepatitis B in the United States and Canada

	Children % (n=343)	Adults % (n=1,625)
Race		
Asia	78	72
Black	11	15
White	9	11
HBV genotype		
A	5	18
B	43	39
C	32	33
D	16	8
Other or multiple	4	4
Presumed mode of transmission		
Vertical	98	60
Horizontal/household	NA	27
Sexual	NA	6

HBV, hepatitis B virus; NA, no data.

of race and HBV genotype. In 2008, the US Centers for Disease Control and Prevention recommended that all persons born in geographic regions with HBsAg prevalence >2% should be tested for chronic HBV infection (5). This includes immigrants, refugees, asylum seekers, and internationally adopted children born in highly endemic countries, regardless of their vaccination status in their country of origin. Moreover, the American Academy of Pediatrics recommended that HBV screening, infection control measures for the adoptees, and counseling for the family adopting the children should be reinforced (6). The majority of adopted children previously resided in orphanages, where they may experience malnutrition, environmental deprivation, neglect, and exposure to infectious diseases before adoption (7). In addition to North America, the burden of imported chronic hepatitis B from Africa and Asia is gradually increasing in children in Australia (8). Under this situation, there are concerns that immigrated children and international adoptees are missing a chance to receive post-arrival screening or are not referred to appropriate medical institutions if HBV infection is identified. These studies indicate that the reinforcement of HBV screening for immigrants and international adoptees and the appropriate medical management of children with chronic HBV infection is an urgent task in children as well as in adults.

Second, it is valuable that the clinical characteristics of HBV genotypes A, B, C, and D were evaluated in children with chronic HBV infection in this pediatric study. The pediatric data on the association between disease outcome and HBV genotypes are limited. The relationship between disease outcome and ethnicity has previously been evaluated in children with chronic hepatitis B. Previous pediatric studies from Canada showed that non-Asian children achieved HBeAg-seroconversion significantly earlier than Asian children (9,10). Although several pediatric studies have been reported, only a few studies have identified the HBV genotype of the infected children. Moreover, only the predominant genotypes in each country could be evaluated (genotype B/C in Taiwan, genotype B/C in Japan, and genotype A/D in Italy and Germany) (11-15). Because the clinical significance of HBV genotypes remains indeterminate in children, the determination of the HBV genotype is not indicated in the algorithm of the recommended approach for monitoring chronically infected children (16) or for the selection of children for antiviral treatment (17). In general, adult studies demonstrate that genotype B is associated with less progressive liver disease than genotype C, and genotype D has a less favorable prognosis than genotype A (18). The current pediatric study showed that a high frequency of HBeAg positivity and high HBV DNA levels were observed in children with genotypes B and C compared to those with other genotypes. A pediatric study from Taiwan reported that genotype B is predominant in children with chronic HBV infection hepatocellular carcinoma, whereas a delay in HBeAg seroconversion occurs in genotype C compared to genotype B (11). Although genotypes A and B are more responsive to IFN than genotypes C and D in adults (19,20), this relationship has not been confirmed in children. A longitudinal study of this pediatric cohort in the US and Canada is expected to clarify the relationship between disease outcome and genotype in children.

Third, one-fourth of children with chronic hepatitis B were born in North America. This finding is consistent with previous reports. In the US and Canada, universal pregnant screening and universal HB vaccination are implemented. However, there is a gap between the recommended protocol and routine practices. The screening rate of pregnant women is approximately 97% in the US (21). Moreover, perinatal HBsAg test results were documented in 93% of maternal medical records; 14% of the infants born to HBsAg-positive mothers were not administered a hepatitis B vaccine, and

20% of infants were born to mothers with an unknown HBsAg status in the US (22). Because testing and reporting are incomplete in the US, the true number of perinatal HBV cases per year is likely to be 10 to 20 times higher (23). In infants born to HBsAg-positive mothers in the US in 2008, the administration rate of HBIG and the hepatitis B vaccine at birth was 96%, and the rate of the completed 3-dose vaccination series by 12 months was 78% (24). A strenuous endeavor to close the gaps between the recommended protocol and routine practices is required in not only the US and Canada but also other countries (25). Even in the era of universal vaccination, careful attention must be paid to the implementation of appropriate management and treatment for children with chronic hepatitis B.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. World Health Organization. Emergencies preparedness, response: hepatitis B. Prevention and treatment. Available online: http://www.who.int/csr/disease/hepatitis/whocdscsrlyo20022/en/index5.html. Accessed December 12, 2015.
2. World Health Organization. Media centre: immunization coverage. Fact sheet No. 378. Available online: http://www.who.int/mediacentre/factsheets/fs378/en/. Accessed December 8, 2015.
3. Schwarz KB, Cloonan YK, Ling SC, et al. Children with Chronic Hepatitis B in the United States and Canada. J Pediatr 2015;167:1287-94.e2.
4. Ghany MG, Perrillo R, Li R, et al. Characteristics of adults in the hepatitis B research network in North America reflect their country of origin and hepatitis B virus genotype. Clin Gastroenterol Hepatol 2015;13:183-92.
5. Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep 2008;57:1-20.
6. Stadler LP, Mezoff AG, Staat MA. Hepatitis B virus screening for internationally adopted children. Pediatrics 2008;122:1223-8.
7. Miller LC. International adoption: infectious diseases issues. Clin Infect Dis 2005;40:286-93.
8. Jimenez G, Alex G, Paxton G, et al. B alert: hepatitis B virus infection in children in Victoria. J Paediatr Child Health 2013;49:E213-6.
9. Marx G, Martin SR, Chicoine JF, et al. Long-term follow-up of chronic hepatitis B virus infection in children of different ethnic origins. J Infect Dis 2002;186:295-301.
10. Popalis C, Yeung LT, Ling SC, et al. Chronic hepatitis B virus (HBV) infection in children: 25 years' experience. J Viral Hepat 2013;20:e20-6.
11. Ni YH, Chang MH, Wang KJ, et al. Clinical relevance of hepatitis B virus genotype in children with chronic infection and hepatocellular carcinoma. Gastroenterology 2004;127:1733-8.
12. Hsu HY, Tsai HY, Wu TC, et al. Interferon-alpha treatment in children and young adults with chronic hepatitis B: a long-term follow-up study in Taiwan. Liver Int 2008;28:1288-97.
13. Komatsu H, Inui A, Sogo T, et al. Chronic hepatitis B virus infection in children and adolescents in Japan. J Pediatr Gastroenterol Nutr 2015;60:99-104.
14. Bortolotti F, Guido M, Bartolacci S, et al. Chronic hepatitis B in children after e antigen seroclearance: final report of a 29-year longitudinal study. Hepatology 2006;43:556-62.
15. Oommen PT, Wirth S, Wintermeyer P, et al. Relationship between viral load and genotypes of hepatitis B virus in children with chronic hepatitis B. J Pediatr Gastroenterol Nutr 2006;43:342-7.
16. Haber BA, Block JM, Jonas MM, et al. Recommendations for screening, monitoring, and referral of pediatric chronic hepatitis B. Pediatrics 2009;124:e1007-13.
17. Jonas MM, Block JM, Haber BA, et al. Treatment of children with chronic hepatitis B virus infection in the United States: patient selection and therapeutic options. Hepatology 2010;52:2192-205.
18. Liaw YF, Kao JH, Piratvisuth T, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. Hepatol Int 2012;6:531-61.
19. Janssen HL, van Zonneveld M, Senturk H, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. Lancet 2005;365:123-9.
20. Flink HJ, van Zonneveld M, Hansen BE, et al. Treatment with Peg-interferon alpha-2b for HBeAg-positive chronic

hepatitis B: HBsAg loss is associated with HBV genotype. Am J Gastroenterol 2006;101:297-303.
21. Schrag SJ, Arnold KE, Mohle-Boetani JC, et al. Prenatal screening for infectious diseases and opportunities for prevention. Obstet Gynecol 2003;102:753-60.
22. Willis BC, Wortley P, Wang SA, et al. Gaps in hospital policies and practices to prevent perinatal transmission of hepatitis B virus. Pediatrics 2010;125:704-11.
23. Ward JW. Time for renewed commitment to viral hepatitis prevention. Am J Public Health 2008;98:779-81.
24. Smith EA, Jacques-Carroll L, Walker TY, et al. The national Perinatal Hepatitis B Prevention Program, 1994-2008. Pediatrics 2012;129:609-16.
25. Hu Y, Zhang S, Luo C, et al. Gaps in the prevention of perinatal transmission of hepatitis B virus between recommendations and routine practices in a highly endemic region: a provincial population-based study in China. BMC Infect Dis 2012;12:221.

Cite this article as: Komatsu H, Inui A. Chronic hepatitis B in children in the United States and Canada: international origins place the disease burden on children even in the era of universal vaccination. Transl Pediatr 2016;5(1):1-4. doi: 10.3978/j.issn.2224-4336.2015.12.08